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# CREATINE SUPPLEMENTATION: A Novel Role in Antioxidant System in Exercise and In Chronic Diseases

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**Abstract**

The effects of creatine supplementation related to ergogenic action which increases maximum strength and body mass has been extensively revised. In the last years it has been hypothesized a novel function of creatine as antioxidant agent. There are few data of this amine on oxidative stress and its role in antioxidant system. A small amount of studies in vitro and in vivo showed promising results related to indirect antioxidant effect, which evaluated the isolated supplementation protocols or added to standard diet. Creatine supplementation seems to exert positive effect on health, mainly in exercise conditions due to the ergogenic action. Furthermore, some evidences suggest that the supplementation might have positive effects on energy metabolism and functional capacity in chronic degenerative diseases. Expressive results were observed in Parkinson's disease and Huntington's disease, in which the creatine might acts as neuroprotective agent, neutralizing the reactive oxygen and nitrogen species action. The modulation of mitochondrial creatine kinase seems to play an important role in reactive oxygen species production, such as radical anion superoxide. This review aims to show the scientific evidences about antioxidant effect of creatine supplementation, when utilized alone or associated with physical exercise, in health individuals and in patients with chronic degenerative diseases.

**Keywords:** Creatine supplementation. Antioxidant. Oxidative stress. Exercise. Chronic disease.

**SUPLEMENTAÇÃO DE CREATINA:**
**Um Novo Papel no Sistema Antioxidante no Exercício Físico e em Doenças Crônicas**

**Resumo**

Os efeitos da suplementação de creatina relacionados com a ação ergogênica das quais aumenta a força máxima e massa corporal tem sido extensivamente revisado. Nos últimos anos tem sido levantada a hipótese de uma nova função da creatina como um agente antioxidante. Há pouca evidência desta amina sobre estresse oxidativo e seu papel no sistema antioxidante. Uma pequena porção de estudos *in vitro* e *in vivo* demonstraram resultados promissores relacionados ao efeito antioxidante indireto, o qual foi avaliado em protocolos de suplementação isolada ou adicionados à dieta padrão. A suplementação de creatina parece exercer efeitos positivos sobre a saúde, principalmente em condições de exercício físico em virtude da ação ergogênica. Além disso, algumas evidências sugerem que a suplementação pode exercer efeitos positivos sobre o metabolismo energético e capacidade funcional em doenças crônico-degenerativas. Resultados expressivos foram observados em doença de Parkinson e doença de Huntington, nas quais a creatina poderia atuar como agente neuroprotetor, neutralizando a ação de espécies reativas de oxigênio e nitrogênio. A modulação da creatina cinase mitocondrial parece desempenhar importante papel na produção de espécies reativas de oxigênio, como o ânion radical superóxido. Esta revisão tem como objetivo demonstrar evidências científicas sobre o efeito antioxidante da suplementação de creatina, quando utilizada, isolada ou associada ao exercício físico, em indivíduos saudáveis e em pacientes portadores de doenças crônico-degenerativas.

**Palavras-Chave:** Suplementação de creatina. Antioxidante. Estresse oxidativo. Exercício. Doenças crônicas.

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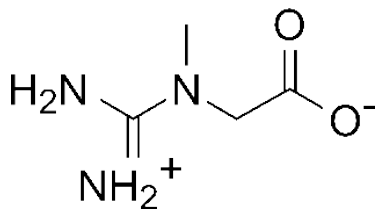
Creatine is a amino acid derived from arginine, glicine and methionine, which is produced mainly by the liver, and in lower proportions, kidneys and pancreas (Figure 1) (Persky; Brazeau, 2001). The creatine has always been present in the feeding of humans, once that is found in high concentrations in meat and fishes (Paddon-Jones; Borsheim; Wolfe, 2004). The use of creatine as a dietetic supplement is based in the possibility to increase creatine storages in skeletal muscles. Creatine-phosphate system or ATP-CrP system (or phosphocreatine) is the predominant energetic system at the beginning of high intensity exercise. The energy transfer occurs by the hydrolysis of a creatine-phosphate molecule (CrP) to water and free creatine (Cr), where occurs the disruption of this enriched energy bound (phosphoric amide), releasing inorganic phosphate grouping (Pi) which will bind to adenosine diphosphate (ADP) forming adenosine triphosphate (ATP) (Branch, 2003; Hespel et al., 2001).

**Figure 1 –** Structural composition of creatine



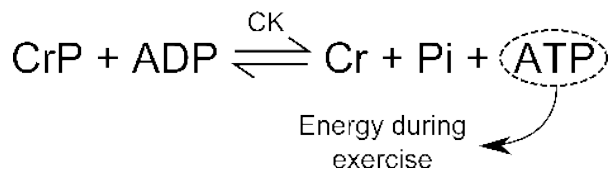

Improvements of energy metabolism during physical exercise associated with dietetic intervention is one of the main interests area among the most physical performance researchers. Creatine supplementation when associated to resistance training, exert positive effects on functional variables, such as muscle endurance, reduction in muscle protein degradation, increase in power output, increase in exercise tolerance and increase in maximum strength. This beneficial effects has been target of investigation since the 1990s (Volek; Rawson, 2004).

It has been speculated a possible antioxidant role of creatine of its direct participation in energy metabolism, especially in skeletal muscle, thereby reducing the formation of reactive oxygen species (Sestili et al., 2011). Oxidative stress is a phenomenon observed in conditions of metabolic imbalance and, predominantly, in situations of strenuous exercise (Fisher-Wellman; Bloomer, 2009), as well as in the development of chronic diseases (Jacob et al., 2013). Therefore, the objective of this review was to address the creatine supplementation as an antioxidant in different scenarios where it is observed a disability of organ systems, due to the overload of exhaustive exercise or in relation to the physiopathological process of certain chronic diseases. This review discusses based on current published literature and our own experience is given. Articles written in English searched in the National Library of Medicine's PubMed MedLine database and in the Web of Knowledge for creatine, exercise, chronic disease and oxidative stress.

## Creatine Kinase System Modulation

To any and each cellular activity, including structural alterations (hypertrophy), a energetic demand to cellular processes is needed, once that this demand is not achieved, cellular biochemical reactions, such as protein synthesis, can be compromised (Van Wessel et al., 2010). To maintaining these sensible processes in metabolic point of view (biochemical), the regulation of reaction speed through the energetic substrate and metabolites concentration needs to be modulated by key-enzymes (Baar et al., 2002). However creatine kinase (CK), responsible enzyme by the catalysis of CrP hydrolysis, exerts direct activity in this reaction, it is located in different compartments of several tissues of the organism (Figure 2) (Wallimann et al., 1992).

**Figure 2 –** Enzymatic reaction catalyzed by the CK and its contribution in energy metabolism. CrP: *Creatine-phosphate*; Cr: Creatine; ADP: *Adenosine Diphosphate*; ATP: *Adenosine Triphosphate*; CK: Creatine Kinase; Pi: *Inorganic Phosphate*.




Once the ATP-CrP system, together with CK activity, may play a complex and polyvalent role in cellular homeostasis (Wallimann; Tokarska-Schlattner; Schlattner, 2011), creatine supplementation in high intensity exercises practitioners enables an enhancement in ATP resynthesis, directly regulating cellular energetic balance in the firsts instants of the exercise (Gotshalk et al., 2008; Willoughby; Rosene, 2001; Volek et al., 1999).

Beyond that, it is reasonable to establish a logical thought that well trained/optimized ATP-CrP system and which does not use $O_2$ in its reactions, does not promote formation of reactive species. Evidences point out that creatine has different micro-compartments. The most prominent effect of the creatine on human organism is over cytosolic energetic buffer.

Dolder et al. (2003) has investigated a possible model of possible protection of creatine over mitochondrial transport permeability. Mitochondrial CK isoform (mtCK) is present in intermembrane space. In situations that the external proportion between ATP/ADP is low, creatine seems to modulate mtCK activity together with mitochondrial energetic balance due to CrP resynthesis in intermembrane space. The ADP formed in this interconversion is internalized to mitochondrial matrix by adenosine transporter. Once internalized, the ATP is resynthetized by $F_0F_1$ ATP-synthase complex (Wallimann; Tokarska-Schlattner; Schlattner, 2011). This mechanism has protective characteristic because it promotes biochemical process maintenance and consequently cellular survival. Some Reactive Oxygen and Nitrogen Species (Rons) may dissemble this process, for this reason it becomes important to evaluate possible antioxidants agents that may attenuate deleterious effects over mitochondria in neurodegenerative pathologies (Jordan; Cena; Prehn, 2003).

## Oxidative Stress and Rons

The definition of oxidative stress is given by the condition that in a very sensible balance between the production of pro-oxidants (free radicals) with the production of antioxidant defenses (antioxidants) by having to occurs imbalance among these two variables, remaining in favor to free radical expression (Fisher-Wellman; Bloomer, 2009). Free radical is, in fact, any species containing one or more unpaired electrons. In cellular processes of energy production, might occur errors in some stages, such as electron chain transporter, in which may occur of 2 to 5% in electron leaking and these links to an oxygen molecule, maintaining an unpaired electron in the electrosphere (Halliwell, 1991). RONS are chemical compounds that do not have unpaired electrons in the electrosphere. It can contribute to free radicals production in biological processes (Halliwell, 2006).

The risk to form free radicals means that these molecules have high reactivity to adjacent biomolecules. The reactions with these reactive species lead to impairment of important cellular structures such as lipid damage (constitutes plasmatic membranes), proteins damage (signaling proteins, enzymes) and nuclear damage (oxidation of nucleic acids) (Finkel; Holbrook, 2000).

## Creatine and its role in antioxidant system

Lawler et al. (2002) investigated the effect of creatine in skeletal muscle, when exposed to different types of oxidant agents, to evaluate its direct or indirect participation on cellular redox state. In this study, the researchers performed experiments in homogenized gastrocnemius of rats, with concentrations found in skeletal muscle with or without creatine supplementation. To expose tissues homogenates to oxidants, creatine has demonstrated to exert antioxidant effect. However, it has demonstrated certain specificity in Rons suppression. Creatine was able to neutralize the action of ionized oxidants in an aqueous medium, such as 2,2'-azino-bis[3-ethylbenzothiazoline-6-suplhonic acid] ($ABTS^+$), anion radical superoxide ($O_2^{\cdot-}$) and peroxynitrite ($OONO^-$), despite to be less effective in suppress these oxidants, when compared to reduced glutathione. However, creatine was not able to neutralize non-ionized reactive oxygen species, such as hydrogen peroxide ($H_2O_2$) and *terc*-buthylhydroperoxide (tB-OOH).

These findings indicates that the creatine seems to exert indirect antioxidant effect, nevertheless, the property of support to others antioxidants (enzymatic and non-enzymatic). In fact, creatine remains disperse in sarcoplasma, which endures the coadjuvant antioxidant in skeletal muscle tissue in activity (De Groof et al., 2002). One limitation of this study was the evaluation of only on gastrocnemius, once remains obscure if creatine exerts similar effect in different tissues where the concentration is also significantly high so.

The potential antioxidant effect of creatine in cell culture submitted to oxidation was evaluated by Sestili et al. (2006), which investigated the result of different strains of cell culture (human promonocyte, endothelial cells and murine myoblasts) exposition to oxidant agents ($H_2O_2$, tB-OOH and $ONOO^-$). The authors observed attenuation in cytotoxic effects caused by oxidant agents in all strains. With these results, cytoprotection was invariably associated to muscle intracellular free creatine content, differently of creatine-phosphate levels. So, this was the first evidence of creatine as antioxidant agent in living cells.

Guidi et al. (2008) evaluated the role of creatine and its antioxidant effect, specifically related to protection on mutagenesis. Nuclear and mitochondrial DNA damage tests were performed in endothelial cells of human umbilical cord. Creatine supplementation showed to exerts a genoprotective activity specifically over mitochondrial DNA. This finding demonstrate an association of mitochondrial DNA protection with genomic stability. The hypotesis to this effect is that creatine could participate in the maintenance of functional consequences in mitochondria, such as oxygen consume, ATP content generation and cell survival.

It is correlated RNA oxidation with the development of cardiovascular and neurological disorders (Martinet et al., 2004; Martinet et al., 2005; Nunomura et al., 2006). It was investigated the exposure to xenobiotics regarding oxidative action differently over RNA and possible protector effect of creatine supplementation. Jurkat leukemic T cells line were treated with ethyl methanesulfonate (EMS), $H_2O_2$, doxorubicin, spermine NONOate and S-nitroso-N-acetylpenicillamine (SNAP). It was observed protection against two oxidative agents: $H_2O_2$ and doxorubicin. This protective specificity of RNA damage might represent an interesting finding in the early stage of development of diseases, once significant alterations at RNA level may bring transcription and translation modifications of essentials for cell metabolism and homeostasis maintenance (Fimognari et al., 2009).

Creatine has been studied for some years mainly related on evaluation of parameters such as cell survival, DNA oxidation (nuclear and mitochondrial) and RNA. For the evidences presented so far, creatine supplementation showed to exert a moderate antioxidant effect on different substrates, still protecting against genetic material in different cellular compartments. These findings brings a new vision of spectrum of activity that creatine might exert *in vivo* and *in vitro* studies (Sestili et al., 2011).

## Antioxidant Effect of Creatine in Physical Exercise

The utilization of creatine supplementation associated to physical exercise has been widely observed due primarily to the ergogenic effect, which increases creatine-phosphate storages, producing increase in maximum strength (Jager et al., 2011). The use of this feature in health subjects, in recommended doses, seems to be safe and effective, since it does not promote harmful effects on hepatic and renal function (Souza et al., 2013; Poortmans et al., 2005).

There are few studies that tried to test the antioxidant effect of creatine in situations where exercise is the stressor factor, which would increase oxidant agents formation. Deminice and Jordao (2012) designed an experiment with creatine supplementation with rats submitted to acute exercise. Consisted in addition of 2% of creatine to the diet, the protocol treated the animals for 28 days and at the end of this period, they were submitted to swimming acute exercise and evaluated in different periods of time after the exercise session (before exercise, immediately after, 2 hours and 6 hours after acute exercise). The investigators observed that creatine supplementation was able to attenuate oxidative stress markers in plasma and muscle in different periods after acute exercise. These data demonstrates that creatine, administered acutely, when present in higher concentrations in plasma in comparison to skeletal muscle, exerts more significant antioxidant effect.

Another work, performed an experiment with two groups of resistance trained men (intensity between 60% and 90% of one maximum repetition): Cr group (4 x 5 g/day of creatine monohydrate) and placebo group (4 x 5 g/day of maltodextrin), during seven days, whose were evaluated the impact of creatine on DNA damage and oxidative stress. There was lower DNA damage

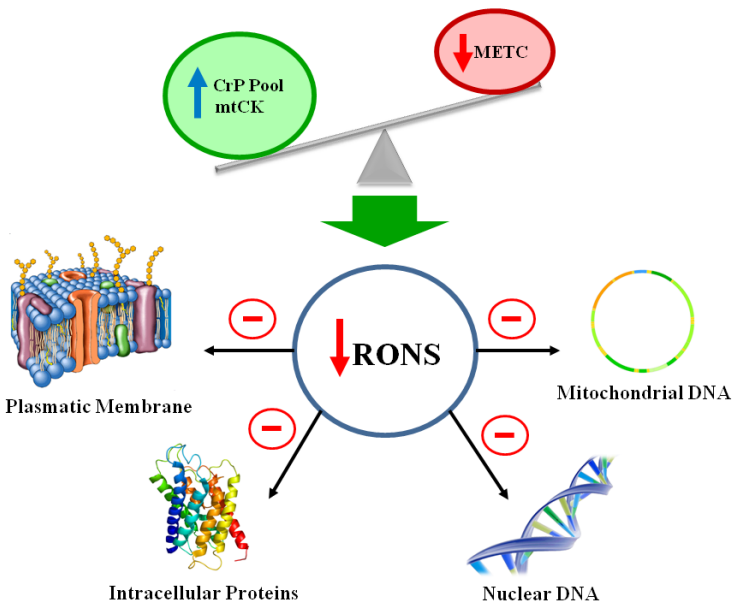
(assessed by 8-hydroxy-2-deoxyguanosine excretion ) and malondyaldehyde plasmatic concentration in the Cr supplemented group (Rahimi, 2011).

Differently from other studies, Silva et al. (2013) evaluated the effect of creatine supplementation in acute eccentric exercise in different periods after exercise in rats (24 hours and 48 hours after exercise session). The investigators submitted the animals to a two-week supplementation protocol of creatine (300 mg/kg/day) and performed a downhill running session until exhaustion. In this study, there was no association between creatine supplementation and decrease in oxidative stress parameters nor increase in antioxidant enzymatic activity in skeletal muscle.

Recently, investigators tested the effects of creatine supplementation along with resistance training in handball athletes after 32 days of protocol (Percario et al., 2012). Trained group that supplemented with creatine (firsts 5 days: 20 g/day, 27 following days: 5 g/day), showed higher increase in uric acid serum concentration and higher decrease in total antioxidant capacity, when compared to control groups. This phenomenon might be explained by the imbalance of the local redox state, leading to higher formation of RONS and, consequently, higher oxidative damage. Despite this induction of oxidative stress in the athletes, they presented superior maximum strength gain to other groups.

The effect of a physical/biological/chemical intervention is feasible to establish a toxicological threshold of response to this stimulus. However, not all interventions have a linear response. In fact, it is necessary to considerate a different type of response to a stimulus, when oxidative stress assessment is at stake, such as hormesis. This latter phenomenon is characterized by a dose-response to several different stimulus in which low-dose of substance administration or physical intervention is stimulatory and high-dose is inhibitory (Calabrese; Baldwin, 2003). In current findings presented previously, it might explain the behavior of creatine supplementation on oxidative damage parameters and possibly the adaptations of antioxidant enzymatic system (Vina et al., 2006). The rationale to explain this hypothesis corroborate with evidences showed above of how creatine supplementation may play a role in situations where oxidative stress is established (Figure 3).

**Figure 3 –** Possible mechanisms for creatine supplementation exerting antioxidant effect. CrP: *Creatine-phosphate*; mtCK: *Mitochondrial Creatine Kinase*; METC: *Mitochondrial Electron Transport Chain*




It is noteworthy to emphasize that in our hypothesis the increasing pool of CrP and mtCK activity might altogether with a reduction of mitochondrial electron transport chain energy contribution in cellular energy metabolism possibly reduces the formation of Rons, protecting several cellular components.

## The Role of Creatine as Ergogenic and Antioxidant Agent in Chronic Degenerative Diseases

In the lasts years has been increasing the interest in studying creatine supplementation in other public beyond athletes and physical exercise practitioners. In some chro-

nic degenerative diseases, mainly in those that can be observed reduction in muscle, cardiovascular, respiratory, neurological and immune function, it has been target of case-control studies and randomized clinical trials. The most studied diseases are those associated with the establishment of chronic oxidative stress and reduction in functional capacity and quality of life of these individuals. It is possible to be found diseases such as muscle dystrophy, heart failure, Parkinson's disease, Huntington's disease and obstructive chronic pulmonary disease (Bender et al., 2005; Faager et al., 2006; Felber et al., 2000; Kuethe et al., 2006; Valastro et al., 2009). Table 1 depicts the different investigations regarding the effects of creatine supplementation in chronic degenerative diseases.

**Table 1 –** Investigations on the effects of creatine supplementation in chronic degenerative diseases.

| Study | Disease (n) | Study Design | Interventions | Outcomes |
|---|---|---|---|---|
| **Andrews *et al.*, 1998** | CHF (20) | Controlled clinical trial | A forearm model of muscle metabolism with handgrip dynamometry (handgrip exercise) for 5min at 25, 30 and 75% of MVC. Creatine supplementation of 20g/day for 5 days. | ↑ Metabolic response for ammonia and lactate.<br>↑ MVC at 75%. |
| **Bender *et al.*, 2005** | HD (20) | Clinical trial | Evaluation of brain metabolite levels pre and post Cr protocol. Supplementation of Cr: 20g/day for 5 days, 6f/day for 8 to 10 weeks. | ↓Glutamate.<br>↓ Unresolved glutamate.<br>↑ Neuroprotection. |
| **Bender *et al.*, 2008a** | HD (162) | Experimental research (mice) | Supplementation of Cr of 1% in normocaloric diet. Two years of experiment to investigate the effect of Cr in aging of an experimental model of HD. | ↑ 9% of survival in supplemented mice.<br>↑ Performance in neurobehaviour tests. |
| **Bender *et al.*, 2008b** | PD (60) | Randomized controlled trial | Long-term supplementation protocol (4g/day) of Cr or placebo for 2 years. | ↔ Renal function.<br>↔Intestinal disorders. |
| **Cornelissen *et al.*, 2010** | CHF (70) | Single center double-blind randomized placebo controlled trial | Three months of exercise training (endurance plus resistance training, 3 sessions per week). Supplementation of 3x5g/day of Cr for one week, 1x5g/day thereafter. | ↔ $VO_2$peak<br>↔ Peak of isokinetic torque (at 60°/s, 110°/s and at 180°/s)<br>↔ LDL and HDL-cholesterol, ↔Triglycerides |
| **Faager *et al.*, 2006** | COPD (23) | Double-blind placebo-controlled trial | Eight weeks of rehabilitation programme with exercise training. Dosage of Cr: 0.3g/kg/day for the first week, 0.07g/kg/day for the remaining 7 weeks. | ↔ Physical performance.<br>↔Grip and knee extensor strength. |
| **Felber *et al.*, 2000** | DMD (1) | Case report | Administration of 155 days of Cr (5g/day) in a 9-year old patient. | ↑ Muscle strength<br>↑ CK activity in plasma. |
| **Fuld *et al.*, 2005** | COPD (38) | Randomized controlled double-blind trial | Twelve weeks of Cr supplementation with pulmonary rehabilitation (5.7g of Cr plus 35g of glucose, 4x/day for 2 weeks, one dose thereafter for 10 remaining weeks). | ↑ FFM.<br>↑ PMS.<br>↑ Health status. |
| **Kuethe *et al.*, 2006** | CHF (20) | Double-blind placebo-controlled with cross-over design | Supplementation of 4x5g/day of Cr for 6 weeks. The patients were crossed-over for the following 6 weeks. | ↑ Body weight.<br>↑ Muscle strength.<br>↔ $VO_2$peak.<br>↔ Ejection fraction. |

| | | | | |
|---|---|---|---|---|
| **Matthews *et al.*, 1998** | HD (81) | Experimental research (rats) | Doses of 0.25 to 3.0% of Cr were added to the diet and 0.25 to 1.0% of CCr were added to the diet in nine different groups for 3 weeks. | ↑ Concentrations of PCr in brain.<br>↓ Peroxynitrite mediated-injury.<br>↓ Hydroxyl radical generation.<br>↓ Neurotoxicity. |
| **Matthews *et al.*, 1999** | PD (100) | Experimental research (mice) | Short-term supplementation of doses from 0.25 to 3.0% of Cr in the diet to evaluate neuroprotection to a PD model in mice. | ↑ Protection against dopaminergic depletion. |
| | MDT1 (34) | Double-blind placebo-controlled with cross-over design | Supplementation of 0.074g/kg/day of Cr and placebo for 4 months. The groups were crossed-over after 6 weeks of wash-out. | ↔ Muscle strength.<br>↔ Body composition.<br>↔ PCr muscle content. |
| | DMD (30) | Double-blind randomized cross-over trial | Supplementation of 0.10g/kg/day of Cr and placebo for 4 months. Six weeks of wash-out to cross-over the supplementation protocols between groups. | ↑ Handgrip strength.<br>↑ FFM.<br>↓DNA oxidative damage.<br>↑ PCr muscle content. |
| **Valastro *et al.*, 2009** | PD (42) | Experimental research (rats) | An experimental model of PD, two groups were treated for 3 weeks with Cr supplementation (diet enriched with 2% of Cr). | ↓ Abnormal involuntary movements.<br>↓ Markers of dyskinesia. |

Cr: *Creatine;* CCr: *Cyclocreatine*; PCr: *Creatine-phosphate*; CHF: *Chronic Heart Failure;* MVC*: Maximum Voluntary Contraction;* HD: *Huntington's Disease;* PD: *Parkinson's Disease*; $VO_2$peak: *Peak of Oxygen Consumption;* COPD: *Chronic Obstructive Pulmonary Disease;* DMD: *Duchenne Muscle Dystrophy;* CK: *Creatine Kinase;* FFM: *Free Fat Mass;* PMS: *Peripheral Muscle Strength;* MDT1: *Myotonic Dystrophy Type 1;* DNA: *Deoxyribonucleic Acid;* ↑ = *improved or increased;* ↔ =*no effect;* ↓ = *reduced.*

## Muscle Dystrophy

Patients with muscle dystrophy presents reduction in protein synthesis and increase in skeletal muscle myofibril degradation. In this form, it becomes necessary to investigate creatine supplementation as coadjutant in treatment in these clinical condition (Felber et al., 2000). Tarnopolsky et al. (2004b) selected thirty one boys (mean of 10 years old) diagnosed with muscle dystrophy that received creatine supplementation (2 to 5 g/day, according to total body weight) during 15 weeks. The placebo group received maltodextrin (dosage) during 15 weeks and then the treatments were swapped for more 15 weeks. It was observed increase in dominating hand grip strength and in lean body mass when supplemented with creatine. Despite of this finding, the same research group performed another study with adults that express myotonic type I muscle dystrophy, supplemented with 5 g/day of creatine monohydrate during 4 months. In the following 6 months they were evaluated without supplementation. The results showed no effect of the supplementation on muscle strength and body composition. However, it has been discussed the possibility of skeletal muscle not have absorbed sufficiently oral creatine, limiting the effects of supplementation on energetic metabolism (Tarnopolsky et al., 2004a). These studies evaluated the possible ergogenic effect of creatine, therefore, it was not assessed antioxidant effect.

## Chronic Heart Failure

The Chronic Heart Failure (CHF) is a syndrome characterized by the inadequate function of the heart in maintaining blood flow necessary to metabolic activities, overcoming prejudice to skeletal muscle function and functional capacity (Bouchla et al., 2011). By these means, it has been tried to evaluate supplementation effect of 20 g/day (4 x 5 g/day) in a five-day protocol associated or not with hand grip exercises on skeletal muscle

metabolism. The protocol demonstrated to be effective in patients with CHF through the upgrade of skeletal muscle metabolism that was observed by ammonia and lactate concentration after voluntary muscle contraction in 75%. Beyond this metabolic response, the individuals that received supplementation, increased maximal contraction strength in 75% to exhaustion (Andrews et al., 1998).

In a recent investigation, researchers evaluated oral supplementation of creatine associated with resistance and endurance training on physical conditioning and cardiorespiratory performance in patients with CHF and coronary arterial disease. The subjects received a standard dosage of 3 x 5 g/day for one week (saturation phase) and a standard dosage of 1 x 5 g/day for the rest of the protocol (maintaining phase). It was not observed differences in physical conditioning and cardiorespiratory performance between the supplemented and control group (Cornelissen et al., 2010). These studies evaluated the ergogenic effect of creatine, however, none assessed oxidative stress parameters.

## Chronic Obstructive Pulmonary Disease

Muscle catabolism evidenced in patients with Chronic Obstructive Pulmonary Disease (COPD) is a multifactorial consequence. There are remarkable features of these patients, such as, reduced food intake, increased energy expenditure, implications of the use of glucocorticoids during treatment and chronic inflammation (Griffiths; Proud, 2005; Layec et al., 2011). Physical training has been a valuable tool in coadjuvant treatment of this pathology. Recently it has been attempted to use not only the physical training, but to combine with it dietary modifications that can improve functional capacity and therefore the quality of life.

The creatine has been studied in rehabilitation of COPD patients. However, none study evaluated oxidative stress parameters, only in functional capacity, despite of has been related in literature that exercise might induce muscle nitrosative stress in patients with COPD (Barreiro et al., 2009). Fuld et al. (2005) performed a randomized clinical trial with creatine supplemented group (n=18, 5.7 g of creatine associated with 35 g of glucose per day) and placebo group (n=20, 40.7 g of glucose per day). Conducted in a double-blind clinical trial, both groups performed a saturation phase (three doses per day), two weeks preceding the pulmonary rehabilitation protocol. The groups underwent a maintenance phase (one dose per day) along with two exercise sessions per week (one hour per day), for 16 weeks. There was an increase in lean body mass, increase in muscle strength and endurance only in the group supplemented with creatine.

From these promising findings, increased the interest to investigate whether this supplement could be utilized in clinical practice. Faager et al. (2006) performed a similar experiment to Fuld et al. (2005). Randomized clinical trial, two groups allocated to creatine or placebo, supplemented for 8 weeks, along with pulmonary rehabilitation program. In this study, the supplementation was not able to improve physical performance differently of the rehabilitation program.

Based on these studies, it was recently conducted a meta-analysis of the efficacy of creatine supplementation in patients with COPD. It was concluded that the supplementation does not affect positively exercise capacity and muscle strength. It is noteworthy to mention that few studies have evaluated these effects, since the majority of these investigations has a small number of patients, once showed methodologies that could be more robust in order to provide more statistically reliable data (Al--Ghimlas; Todd, 2010).

## Parkinson's Disease

The major pathologic consequence of Parkinson's disease is associated with dopaminergic neurons death in the substantia nigra. Several environmental toxins (pesticides, herbicides) were related with the disease and to a lesser extent, genetic factors present themselves as being responsible for the onset of neurological degeneration (Kones, 2010). Creatine is considered to be a neuroprotective agent due to its ability to mitigate the rate of ATP depletion by increasing intracellular concentration of CrP, which becomes important in synaptic activity and in skeletal muscle metabolism (Chao et al., 2012). There is possibly a partial contribution of NA-

DPH oxidase system in $O_2^{\cdot-}$ formation, as observed in a experimental model of Parkinson's disease, which suggested that this same energy system could be responsible for neuronal degeneration (Block; Zecca; Hong, 2007; Wu et al., 2005).

In another work, Parkinson's experimental model as well Matthews et al. (1999), mices were supplemented with creatine monohydrate and cyclocreatine (from 0.25% to 3.0% of creatine added in diet) for two weeks, to evaluate neuroprotective effects, against the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahtdropyridine neurotoxin (MPTP). It was observed protection against dopaminergic depletion induced by MPTP in both groups supplemented with creatine, as in the groups that received cyclocreatine.

More recently, Bender et al. (2008b) evaluated in a randomized clinical trial the effect of long term creatine supplementation (two years) on collateral effects and kidney function in elderly diagnosed with Parkinson's disease. The subjects were divided in two groups: supplemented with creatine (Cr – firsts 6 days, 20 g/day; 2 g/day for 6 following months and 4 g/day for the rest of the study, n=40) and placebo (Pla – firsts 6 days, 20 g/day; 2 g/day for 6 following months and 4 g/day for the rest of the study, n=20). In relation to adverse effects on gastrointestinal symptoms, only 29% of the patients that received creatine presented symptoms. There were no other adverse significant effects during the study, however, there was an increase in serum creatinine in the supplemented group. In elderly populations, creatine supplementation seems to be a safe strategy as coadjutant therapy in the treatment of Parkinson's disease.

## Huntington's Disease

Being an inherited neurological disorder, whose consequence is the exacerbation of excitotoxicity in Huntington's Disease (HD) causes an aggressive scenario, in greater proportion, the neurons of the substantia nigra and prefrontal cortex. Mitochondrial damages, involving energy metabolism results in increased formations of RONS. These reactive species sustain a vicious cycle of mitochondrial damage and decreased cellular bioenergetic, making unfeasible to cell survival, which induces neurodegeneration in patients with HD (Ayala-Pena, 2013).

In a experimental research with mices (Control, n=81; Creatine, n=81) that received creatine by feeding (1% of diet; normocaloric in both groups). The investigators performed in every 12 weeks tests to evaluate the presence of microorganisms. After 24 months with differentiated diet maintenance between the control and creatine group, it was observed higher cumulative survival of approximately 9% in the group that received creatine by feeding. The discussion of this finding of antiaging relies on the possible suppression of oxidative stress in these animals (Bender et al., 2008a).

When animals with experimental model of HD were submitted to malonate exposure, supplementation of creatine (Cr) and cyclocreatine (CCr) were able to attenuate lactate concentration in striatal regions (metabolite characteristic of neurodegeneration). The investigators established ranges of supplements added to the diet for the groups creatine (0.25% to 3% of Cr) and for the groups of cyclocreatine (0.25% to 1% of CCr). The range that replied an improved reduction of 3-nitropropionic acid, a marker of $ONOO^{-}$ mediated injury, was the group that received 1% of Cr added to the diet (Matthews et al., 1998).

The increase of the activity of glutamatergic neurons disperses in several structures of central nervous system, such as the basal nuclei and cortical regions, are related to the framework of neurodegenerative disorders. Bender et al. (2005) supplemented 20 patients with creatine (20 g/day for five day, 6 g/day for the rest of the protocol) for 8 to 10 weeks. In this small group, there was a decrease in glutamate levels, indicating that the supplementation might increase Cr and CrP concentrations and consequently would exert neuroprotective effect, specifically by reducing neuronal excitotoxicity. However, oxidative stress parameters were not evaluated in this study.

## Conclusions

It is clearly that the creatine supplementation exerts ergogenic effects in healthy individuals. In different situations, such as degenerative diseases, the same outcome

can be observed. However, depending on the disorder, its mechanism of action of benefit might differ. In *in vitro* and *in vivo* studies was demonstrated that the supplementation of creatine exerts a significant antioxidant effect in specific diseases and when associated with physical exercise (acutely and chronically). Creatine may affect directly the CK system modulation in order to reduce the needing to utilize more mitochondrial activity from the electron transporter chain and utilize in higher proportions the ATP synthesis from ATP-CrP system, which is present in several cellular microcompartments. In the present study we showed what has been investigated regarding creatine supplementation. Different studies shows is that creatine supplementation might be an interesting coadjutant tool for the treatment of different chronic degenerative diseases.

## Declaration of Interest

The authors report no conflict of interest.

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